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## **A core outcome set for clinical trials of chemoradiotherapy**

### **interventions for anal cancer (CORMAC):**

#### **A patient and health care professional consensus**

Rebecca Fish, FRCS<sup>1,2</sup>; Caroline Sanders, PhD<sup>3</sup>; Richard Adams, FRCR<sup>4,5</sup>; Julie Brewer<sup>2</sup>, Sara T. Brookes, PhD<sup>6</sup>; Jill DeNardo<sup>2</sup>; Rohit Kochhar, FRCR<sup>2</sup>; Mark P. Saunders, PhD<sup>2</sup>; David Sebag-Montefiore, FRCR<sup>7</sup>; Paula R. Williamson, PhD<sup>8</sup>; Andrew G. Renehan, PhD<sup>1,2,9\*</sup>  
\*Joint senior authors

1. Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Vaughan House, Portsmouth Street, Manchester, M13 9GB.
2. Colorectal and Peritoneal Oncology Centre, Christie NHS Foundation Trust, 550 Wilmslow Road, Manchester, M20 4BX.
3. Centre for Primary Care, University of Manchester, Williamson Building, 6<sup>th</sup> Floor, Suite 3, Manchester, M13 9PL.
4. Centre for Trials Research, Cardiff University School of Medicine, UHW Main Building, Health Park, CF14 4NX.
5. Velindre Cancer Centre, Velindre Road, Whitchurch, Cardiff, CF14 2TL.
6. Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, B15 2TT.
7. University of Leeds, Leeds Cancer Centre, St James University Hospital, Beckett Street, Leeds LS9 7TF.
8. MRC North West Hub for Trials Methodology Research, Department of Biostatistics, Block F Waterhouse Building, University of Liverpool, 1-5 Brownlow Street, Liverpool, L69 3GL.
9. Manchester Cancer Research Centre and NIHR Manchester Biomedical Research Centre, University of Manchester, Manchester

#### *Running title:*

*Core outcome set for anal cancer clinical trials*

#### Correspondence to:

Ms Rebecca Fish  
Clinical Research Fellow  
Division of Cancer Sciences, School of Medical Sciences  
Faculty of Biology, Medicine and Health  
University of Manchester  
Vaughan House, Portsmouth Street  
Manchester, M13 9GB.  
07917157242  
E-mail: [rebecca.fish-2@manchester.ac.uk](mailto:rebecca.fish-2@manchester.ac.uk)

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## **SUMMARY**

Chemo-radiotherapy is primary treatment in patients with squamous cell carcinoma of the anus (SCCA) but variations in trial outcome reporting have limited between-study comparisons and hindered evidence synthesis. Treatment-related morbidity is considerable, yet no trial has comprehensively quantified long-term side-effects or quality of life. To address these issues, we established the first international health care professional (HCP)-patient consensus to develop a core outcome set, using the COMET methodology. We conducted a systematic review and patient interviews to derive a comprehensive list of outcomes, followed by a two-round Delphi survey completed by 149 participants from 11 countries (patients, 55; HCPs, 94). The Delphi results were discussed at a combined HCP-patient consensus meeting, where agreement was reached on 19 core outcomes across four domains: Disease activity, survival, toxicity, life impact. Implementation of the Core Outcome Research Measures in Anal Cancer (CORMAC) set in future trials will serve as an overall framework to capture a core of relevant, standardised outcomes across four domains, facilitate selection of health area-specific evaluation tools; reduce redundancy of lengthy outcome lists; allow outcome comparisons; and ultimately enhance the relevance of trial findings to HCPs, trialists and patients.

## **INTRODUCTION**

The incidence of squamous cell carcinoma of the anus (SCCA) has increased globally over the last 3 decades<sup>1</sup>, most markedly in high income countries, where (world) standardised incidence rates range from 0.4 to 1.8 per 100,000. Historically, primary treatment of SCCA was by radical surgical resection, but a paradigm shift occurred in the 1970s and 1980s when small studies demonstrated high rates of local control with primary radiotherapy, with or without chemotherapy,<sup>2,3</sup> and an opportunity for anal sphincter preservation. Subsequently, six phase III randomised trials (2877 patients) in Europe and the USA established the effectiveness of chemoradiotherapy as primary treatment.<sup>4-9</sup> Over this period, survival progressively improved; currently 5-year overall survival rates approach 75%.<sup>10</sup> However, this success has come at the cost of considerable treatment-related acute and long-term toxicity. Across the above six trials, there is considerable variation in trial outcome reporting limiting between-study comparisons and hindering evidence synthesis.<sup>11</sup> Furthermore, outcomes in these trials were primarily related to survival and disease activity; no trial comprehensively addressed long-term side effects or quality of life (QoL). Both of these issues can be addressed by the development of a core outcome set (COS) “an agreed, standardised set of outcomes to be measured and reported, as a minimum, in all trials in a particular health area”<sup>12</sup>. COS have been endorsed as a means to reduce outcome heterogeneity, and to increase the relevance of research through involvement of key stakeholders in COS development<sup>13</sup>. This paper describes the development of a COS for trials of chemo-radiotherapy interventions for SCCA.

## **METHODS**

### *Scope*

The scope of the core outcome set to be developed has been defined according to the criteria recommended by COMET <sup>14</sup>.

**Health condition:** Non-recurrent, non-metastatic squamous cell carcinoma of the anus/ anal canal (SCCA)

**Population:** Adults >18 years of age

**Types of Interventions:** Primary treatment with chemoradiotherapy

**Setting:** Later phase trials that will inform clinical decision making

#### *Study overview*

The COS was developed in three phases, inclusive of patients and health professionals at each stage: (1) A long-list of outcomes was generated through systematic review<sup>15</sup> and semi-structured patient interviews; (2). The outcome long-list was used to populate the 2-phase Delphi process; (3) The results of the Delphi survey were reviewed at a face-to-face consensus meeting and a final COS determined.

#### *Phase 1: Information Gathering*

##### **Search strategy and selection criteria**

Full details of the systematic review, including search strategy, databases and selection criteria have been published elsewhere.<sup>15</sup> Outcomes and accompanying definitions were extracted verbatim from included studies and categorised into domains.

##### **Semi-structured interviews**

Outcomes of importance to patients were identified through semi-structured interviews. This approach uses open questions to facilitate a patient-led discussion, guided by additional prompts from a pre-prepared topic guide to ensure key areas are covered. Patient participants for the semi-structured interviews were identified and recruited from the Christie NHS Foundation Trust (Manchester, United Kingdom) anal cancer database and through the Macmillan anal cancer forum,<sup>16</sup> following a purposive sampling matrix defined a priori. Eligibility criteria and the sampling matrix are available in the study protocol.<sup>17</sup> Written informed consent was obtained before interviews. Outcomes were identified both indirectly through

listening to patients' experiences and directly by asking about information needs before, during and after treatment. Audio recordings of the interviews were transcribed in full and coded to identify outcomes.

### **Long-list generation**

Outcomes from the systematic review and patient interviews were combined. The long-list of outcomes, accompanied by relevant quotes from the patient interviews, was discussed by the CORMAC Study Advisory Group (SAG, described below) (September 2017). For each outcome, the group agreed (i) merging with closely related items and; (ii) exclusion if considered to be of limited clinical importance (for example, extremely rare events) and were not identified in the patient interviews. (iii) face validity and domain allocation. The final outcome list was used to populate the Delphi questionnaire. Outcomes were converted into question items, with clinical and plain language versions, which were reviewed for face validity, understanding and acceptability by the Christie NHS Foundation Trust Patient Information Committee (comprising health professionals and lay members) and modified according to feedback.

### *Phase 2: Delphi Survey*

The Delphi survey was run using the online DelphiManager platform.<sup>18</sup> Participants were recruited from the two key stakeholder groups: patients and health care professionals (HCPs). Clinical researchers involved in clinical trials formed a subgroup within the HCP stakeholder group. Patients were recruited from four UK treatment centres, via social media (Twitter) and patient advocacy groups (Supplementary file S1). Patients were asked to confirm that they had received or were receiving treatment with chemoradiotherapy for SCCA in a declaration when registering to take part in the Delphi. HCPs were recruited by direct e-mail to principal investigators in the PLATO (PersonaLising Anal cancer radioTherapy dOse) trial<sup>19</sup> and via UK and international professional organisations (Supplementary file S1). Eligibility criteria are detailed in the study protocol. The Delphi process was conducted over 2 rounds (termed R1 and R2). In each round, participants were asked to rate the importance of including each

outcome in the COS on a 1-9 scale described as: Limited importance (1-3); important but not critical (4-6); and critically important (7-9). Participants could suggest additional outcomes at the end of R1 which were reviewed by the core team (RF, CS, AGR and PRW); any outcome not already represented was added to R2. No outcomes were dropped between rounds. In R2, participants were shown a histogram of the R1 scores for each outcome together with their own R1 score, before being asked to reflect on the information presented and score each outcome again.

The percentage of participants scoring each of 1-9 was calculated from the R2 scores for each outcome. Consensus criteria were defined a priori:<sup>12</sup> outcomes scored as 'critically important' (7-9) by  $\geq 70\%$  of patients and  $\geq 70\%$  of HCPs, and 'limited importance' (1-3) by  $\leq 15\%$  of patients and  $\leq 15\%$  of HCPs were defined as 'consensus in' and included in the provisional COS. Outcomes scored 1-3 by  $\geq 70\%$  and 7-9 by  $\leq 15\%$  of both stakeholder groups were defined as 'consensus out' and were excluded. Outcomes not fulfilling criteria for consensus in or out were defined as 'no consensus'.

### *Phase 3: Consensus Meeting*

The results of the Delphi survey were presented at a face-to-face consensus meeting. Participants were eligible to attend if they had completed both rounds of the Delphi survey. Participants were sampled purposively to promote balanced representation of patients and HCPs of differing disciplines. International participation was capped for budgetary reasons. Prior to the meeting, all participants were sent a summary of their own Delphi R2 scores. The meeting was chaired by an independent, non-clinical researcher with expertise in COS development methodology (SB), and not a member of the SAG.

Outcomes identified in R2 of the Delphi as 'consensus in' were presented first and participants asked if there were any fundamental reasons why these should not be included in the COS. Outcomes deemed 'consensus out' were reviewed and participants asked if there were any fundamental reasons why these should be included in the COS. All 'no consensus' outcomes were discussed and voted on with outcomes where one stakeholder group had scored  $\geq 70\%$

7-9 considered first. Remaining 'no consensus' outcomes were reviewed together, with individual outcomes being discussed and voted on only if proposed as being important by a meeting participant. Contrasting views were actively sought and the chair ensured all participants had equal opportunity to contribute before voting commenced. Voting was conducted anonymously using TurningPoint® software and handsets (Turning Technologies LLC, Youngstown, USA). Voting followed the same format as in the Delphi, with results displayed to participants immediately for each outcome. Outcomes meeting the criteria for 'consensus in' were included in the COS; all other items were dropped. At the end of the meeting, the final COS was presented to participants and ratified.

#### *Other analyses*

We assessed for attrition bias between Delphi R1 and R2, comparing the distribution of mean R1 scores for participants did and did not complete R2<sup>12</sup>. We assessed for consensus meeting participation bias by comparing the distribution of mean R2 scores for participants who did and did not participate in the consensus meeting. To assess satisfaction with the process and outcome of the consensus meeting, we collected questionnaire feedback from participants, (Supplementary file S2).

#### *Ethics and registration*

Our findings are reported in line with the Core Outcome Set-Standards for Reporting (COS-STAR) reporting guidance.<sup>20</sup> This project was prospectively registered with the COMET initiative (Core Outcome Measures in Effectiveness Trials).<sup>21</sup> The study protocol and composition of the SAG have been published elsewhere.<sup>17</sup> The study was approved by the National Research Ethics Service: Semi-structured interviews: IRAS ID 183034, CPMS study ID 20368, adopted January 2016; Delphi and consensus meeting: IRAS ID 215791, CPMS Study ID: 33052; adopted February 2017.



## RESULTS

An overview of the CORMAC COS development process and of the final COS is shown in figure 1.

### *Phase 1: Information Gathering*

The systematic review has been described in detail elsewhere [16]. In brief, 1243 outcomes were identified from 101 studies, consolidated into 92 standardised outcome terms. Interviews with 19 patients identified ~~64~~<sup>57</sup> outcomes, including eight not identified from the literature (skin pain, skin itch, sleep disturbance, bone/joint pain, fertility, menopause, ejaculatory function and orgasmic function). The 100 standardised outcome terms were categorised into five domains (survival; disease activity; life impact; delivery of care; and toxicity), which can be directly mapped to the outcome domain taxonomy recommended by COMET<sup>22</sup>. After discussion by the SAG, 73 standardised outcome terms were taken forward into the Delphi process; one outcome was expanded into two and 28 were removed. Full details of the outcomes excluded along with the reasons are available in supplementary file S3.

### *Phase 2: Delphi Process*

One hundred and forty-nine participants from 11 countries (patients 55; HCPs 94) completed both rounds of the Delphi process. Participant characteristics are shown in Table 1. Thirty additional outcomes were proposed during R1, of which five were added into R2, and two outcome descriptions were revised (supplementary file S4). The full list of Delphi question items is available in supplementary file S5.

The R2 results are summarised in Table 2. Fourteen outcomes met the criteria for 'consensus in'. No outcomes met the original criteria for 'consensus out' so it was agreed by the SAG to redefine the criteria for 'consensus out' to a majority rule; outcomes were classed as 'consensus out' if  $\leq 50\%$  of participants in both stakeholder groups scored the item as critically

important (7-9). Thirteen outcomes met the revised criteria for 'consensus out'. The Delphi R1 and R2 scores individual outcome are shown in supplementary file S6 and S7.

The attrition rate from R1 to R2 was 18% (14% HCPs; 25% patients). Comparison of mean R1 scores for participants who did and did not complete both rounds suggested that those who did not complete R2 may have been more likely to score all outcomes more highly than those continuing to R2 (Figure 2A).

### *Phase 3: Consensus Meeting*

Twenty-three HCPs and 13 patients participated in the consensus meeting (supplementary file S8). Comparison of the mean R2 scores of participants attending to those not attending the consensus meeting shows no evidence of any participation bias (Figure 2B).

During discussions, participants suggested that different aspects of sexual function may be important to different people, with the result that no individual outcome would reach the threshold for inclusion despite broad agreement that sexual function overall should be included. Participants proposed and agreed through voting that all sexual function related outcomes be grouped together under a single broader outcome 'sexual function'. This term mirrors other functional outcomes considered (physical, emotional, role/occupational and social function). This was subsequently validated on examination of the R2 results, which show that 80% (44/55) of patients and 71% (67/94) of HCPs scored 7-9 for at least one outcome in the sexual and reproductive toxicity domain.

The results of voting for each outcome are shown in Table 3. The new 'sexual function' outcome and 4 'no consensus' outcomes from the Delphi reached the criteria for 'consensus in' and were included in the final COS. Six outcomes that did not reach the threshold for 'consensus in' were scored as critically important (7-9) by  $\geq 70\%$  of patients (cognitive function, emotional function, occupational/role function, anal pain, gastrointestinal (anorectal) bleeding and vaginal toxicity).

During analysis of the consensus meeting voting results, we noted one HCP had erroneously self-allocated to the patient group. If they had selected the correct stakeholder group, it is

possible that one outcome (sexual function) may not have reached 70% 7-9 in the HCP group and would therefore not have been included in the COS. Since only one out of the 14 participants in the self-allocated patient group scored this outcome less than seven, the probability of correct self-allocation changing the results is only 7% (1/14). Additionally, the final core outcome set was reviewed and agreed by all participants at the close of the consensus meeting. We therefore recommend that the original results stand.

The final COS (Figure 1) includes 19 outcomes across four domains (6 disease activity; 5 survival; 5 toxicity; 3 life impact). These were: treatment response, local failure, regional failure, distant failure, disease progression, salvage surgery, overall survival, cancer-specific survival, disease-free survival, metastasis-free survival, progression-free survival, anal incontinence, faecal urgency, pelvic fistula, stoma, skin loss, physical function, sexual function, and health-related QoL.

The feedback questionnaire was completed by 74% (17/23) HCPs and all patients. All patient participants and 16/17 HCPs were comfortable communicating their views during the meeting (one HCP was ambivalent). All patients and 15/17 HCPs agreed that the meeting produced a fair result. The remaining HCPs deferred judgement until the final report was produced. Participants from both stakeholder groups commended the meeting for facilitating discussion between HCPs and patients.

## **DISCUSSION**

### *Main findings*

Our study is the first international combined HCP-patient consensus on outcomes for trials in SCCA. All the included outcomes were all identified as critically important by over 70% of both patients and HCPs, using consensus methods which ensured representation of these groups on an equal footing. We recommend that all future trials evaluating chemo-radiotherapy for SCCA utilise the COMRAC COS as a framework for outcome selection.

*In context with other literature*

We have not identified any other published COS for anal cancer. Glynne-Jones et al<sup>23</sup> previously identified the need for consensus on outcome definitions in anal cancer trials, but made recommendations based on the view of the authors without direct involvement of patients or the wider community of HCPs. In contrast, both patients and a broad range of HCPs have been involved in each stage of the development of this COS.

In our initial systematic review linked to this consensus,<sup>15</sup> we identified more than ten different survival or survival composite outcome terms in use, all with varying definitions. With the exception of overall survival, no survival outcome was reported in every randomised trial, and none has a single agreed definition. This heterogeneity reflects the lack of consensus (until now) on which survival endpoints to capture other than overall survival.

There were some unexpected inclusions and exclusions in the final COS. Colostomy-free survival, which has been commonly used in trials in this field, was not selected as a core outcome, but colostomy was. This illustrates the pitfalls of creating composite outcomes; even when the events used to create a composite outcome are of interest, relevance of the composite cannot be assumed. The difficulties of defining progression-free survival (PFS) and its validity as marker for improved survival or QOL have been widely discussed,<sup>11,15,24-26</sup> however PFS is included in the CORMAC COS, indicating that it holds relevance to both patients and HCPs. In the next phase of the project, we will work to agree standardised definitions for the included outcomes.

The new EORTC QOL module, ANL-27,<sup>27</sup> is an anal cancer-specific patient reported outcome measure (PROM) developed and validated in a large international cohort of patients, which identifies the patient reported toxicity and functional outcomes which impact HRQOL in SCCA. The EORTC project aimed solely to evaluate the factors influencing HRQOL and did not evaluate patient (or HCP) views on survival or disease activity outcomes. By contrast, the present COS will serve as an overall framework to capture a wide range of agreed outcomes

in future trials. The outcomes in the CORMAC COS were derived through a transparent, inclusive, consensus process, from a comprehensive list of all possible outcomes, generated through systematic review and interviews with patients. The 19 outcomes included in the final COS (Figure 1) fall across four domains.

#### *Strengths and limitations*

The CORMAC study has a number of strengths. Our methodology is coherent with recommendations from an international consensus,<sup>28</sup> and was clearly defined a priori in a protocol.<sup>17</sup> Inclusion of both patients and HCPs at every stage ensured that outcomes in the final core set fairly represent their shared priorities. A unique strength of our consensus meeting, highlighted in the participant feedback, was directly bringing together patients and HCPs, enabling each group to hear the others' views, facilitating open discussion. We ensured that the views of both stakeholder groups were represented equally, despite difference in the number of participants in each group, by applying the same consensus criteria to electronic voting as was used in the Delphi survey. Our comprehensive and rigorous longlisting process ensured that outcomes across all domains (survival, disease activity, life impact including HRQOL, toxicity and delivery of care) were considered during the consensus process.

There are some limitations to this study. Due to time and budgetary constraints, our project was conducted only in English. Despite this, our Delphi process included patient and HCP participants from 11 countries. The attrition rate for patient participants in the second round of our Delphi is slightly higher than in other recent COS projects,<sup>29-31</sup> possibly affected by the recruitment methods used. To maximise international reach, we disseminated Delphi invitations via social media and group e-mails through patient advocacy groups, with 62% of all patient participants being recruited via these channels. This group had the highest attrition rate, 33%, compared to 15% in those recruited via hospital sites, suggesting that participants recruited in this way are not as invested in the process as those recruited through personal contact.

#### *Clinical implications*

It is important to acknowledge the interplay between outcomes in the toxicity and life impact domains. The toxicity domain relates to physiological outcomes including symptoms, whereas the life impact domain relates to the functional items and composite measures of HRQOL. At the consensus meeting, both HCPs and patients described the functional impact of the included toxicity outcomes. However, patient participants also described the value of specific toxicity outcome data, for example, the incidence and duration of symptoms, in addition to measures of impact. Therefore, we feel that it is important to maintain the distinction between these two domains.

The life impact outcomes in the CORMAC COS include physical and sexual function as well as the composite measure of HRQOL. It is likely that the life impact and toxicity outcomes included in the CORMAC COS are factors in HRQOL in SCCA, but identifying the determinants of HRQOL was not the aim of this project and there are outcomes not included in the COS which influence HRQOL, as demonstrated by ANL-27.<sup>27</sup> The concordance between the toxicity and life impact outcomes included in the CORMAC COS and the question items included in ANL-27 makes it likely that ANL-27 will be recommended as the preferred measurement instrument for these core outcomes. However, definitive recommendations cannot be made until full evaluation of available instruments has been completed in next phase of the CORMAC project.

There were six outcomes that were not included in the final COS that at the consensus meeting were rated as critically important by patients, but not critically important by HCPs (Table 3). However, a COS is a *minimum* set of outcomes that should be included in trials in a particular field. The issues identified as of key importance to patients, including those not reaching the threshold for inclusion in the COS, can be used to aid the selection of additional outcomes of interest and to guide the research agenda going forward. A COS should also be reviewed periodically to determine whether any excluded outcomes should be added or any included outcomes removed.<sup>12</sup>

### *Patient reported outcome Measures (PROMs) in Oncology*

Toxicity outcome reporting in trials for SCCA interventions and in oncology in general has historically been poor, with toxicity outcomes frequently reported only in non-specific terms such as 'gastro-intestinal toxicity' or 'acute toxicity'.<sup>15</sup> The clinician-reported CTCAE (Common Terminology Criteria for Adverse Events) system is the most widely used tool for measuring toxicity in oncology trials<sup>32</sup>, including anal cancer trials<sup>15</sup>. However, there are no guidelines for the clinical application of a given toxicity grading system, such as methods of patient screening or data collection<sup>33</sup> and trial reports rarely describe these methods in any detail.<sup>33</sup> Clinician reporting of symptomatic toxicity outcomes has been shown to lack reliability<sup>34</sup> and under-estimate the incidence and severity of symptoms compared to patients' direct reports.<sup>35-37</sup> Recognition of these issues has led to the development of new instruments for direct patient reporting of toxicity outcomes, such as PRO-CTCAE<sup>38</sup> and eRAPID.<sup>39</sup> However, such patient-reported outcomes measures do not necessarily include patient-important outcomes, and the issue of selecting which toxicity outcomes to measure in a given trial has yet to be adequately addressed. The eRAPID system has selected a number of outcomes frequently experienced during treatment for five of the most common cancers. Therefore, toxicities encountered during treatment for rare cancers, such as anal cancer, may not be represented. The PRO-CTCAE system is derived from the CTCAE and includes a comprehensive library of 124 symptomatic toxicity outcomes from which trialists can construct bespoke PROMs by selecting applicable question items. To-date, there are no recommended outcome subsets specific to SCCA. By identifying the toxicities of critical importance to patients and HCPs, the CORMAC COS will facilitate selection of health area-specific evaluation tools in future trials increasing relevance and reducing redundancy.

### *Future challenges and research*

Efforts will be needed to promote and monitor uptake of this COS. The COMET Initiative works to promote COS utilisation,<sup>40</sup> and trial funding bodies, regulatory authorities and guideline development groups, such as the (UK) National Institute for Health Research, the European

Medicines Agency and the (UK) National Institute for Health and Care Excellence, now actively endorse the use of COS. Searches of trial registries<sup>41,42</sup> identify five phase II and two phase III clinical trials of interventions for SCCA that are recruiting or opening soon. We recommend that the trial management groups (TMGs) of these studies review the CORMAC COS to consider if any changes to trial outcome measurement should be made to accommodate the recommended core outcomes. The most recent of the phase III trials, PLATO,<sup>19</sup> commenced recruitment in the United Kingdom in 2017 and aims to evaluate both dose de-escalation in early stage and dose escalation in locally advanced disease. There is already considerable overlap between the outcomes specified in the PLATO trial protocol and the CORMAC COS.

Development of this COS involved participation of stakeholders from 11 different countries, however further work should be undertaken to validate this COS more widely, especially in non-English speaking populations. Finally, the CORMAC COS describes which outcomes should be included in future clinical trials in SCCA. To ensure quality and consistency in measurement and reporting of these outcomes, in the next phase of this project we will work to agree standardised definitions and recommended measurement instruments for each outcome in the COS, following the approach recommended by the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments)/COMET collaboration.<sup>43</sup>

### *Conclusion*

The outcomes included in the CORMAC COS represent the consensus opinion of an international group of patients, healthcare professionals and trialists and addresses an unmet need, assisting trialists in the design, conduct and reporting of future trials. Implementation of the CORMAC COS will ultimately enhance the relevance of trial findings to HCPs, trialists and patients.





#### **AUTHORS CONTRIBUTIONS**

AGR and PRW conceived the project. AGR and PRW are the joint principal investigators for the study. RF is the clinical research fellow and is responsible for management of the project. RF conducted the systematic review, Delphi process and convened the consensus meeting. AGR, PRW and CS provided supervision and have had input to all aspects of the project. AGR and PRW provided guidance on the systematic review, PRW provided guidance on the Delphi process and consensus meeting and CS provided guidance on the patient interviews and qualitative analysis. RA, JB, JDN, RK, MS and DSM formed the CORMAC study advisory group (SAG) and along with AGR, CS and PRW contributed to the preparation of material for population of the Delphi questionnaire. DSM was a lead member of the SAG and supervised the formulation of clinical descriptions of disease activity and survival outcomes used in the Delphi. The SAG and AGR participated in the consensus meeting. SB chaired and contributed to the planning of the consensus meeting with RF and PRW. CS and PRW assisted with facilitation of the consensus meeting. RF wrote the first draft of the manuscript and SB, CS, DSM, AGR, PRW and have critically revised the manuscript. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

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#### **CORMAC STUDY ADVISORY GROUP**

Professor Andrew Renehan (Professor of Cancer Studies and Colorectal Surgeon), Dr Caroline Sanders (Reader in Medical Sociology), Professor Paula Williamson (Professor of

Biostatistics and co-founder of COMET initiative), Dr Rohit Kochhar (Radiologist), Mrs Julie Brewer (Specialist Nurse), Mrs Jill De Nardo (Patient Representative), Professor David Sebag-Montefiore (Professor of Clinical Oncology and Health Research), Professor Richard Adams (Professor of Clinical Oncology and Trials Research), Dr Mark Saunders (Clinical Oncologist)

#### **CONSENSUS MEETING PARTICIPANTS**

Andrew Renehan; Graham Branagan; Sara Brookes (chair); Martyn Evans; Nancy Baxter; Neil Smart; Nicola Fearnhead; Peter Coyne; Rachel Hargest; Rick Saunders; Tamzin Cumming; David Sebag-Montefiore; Ian Geh; Luc Dewitt; Marianne Guren; Mark Saunders; Rachel Cooper; Victoria McFarlane; Angela Betsworth; Carol Sleith; Ian Curtis; David Crowe; Dean Nixon; Debbie Daley; Elaine Hughes; Helene Hutchings; Jill De Nardo; Lynne Atwood; Maggie Llewellyn; Sarah March; Lindy Berkman; Lucy Davidson; Catherine Grierson; Vicky Goh; Ane Appelt; Julie Brewer; Julia Young

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#### CONFLICT OF INTEREST STATEMENTS

PRW is a member of the COMET management group. All other authors declare they have no competing interests.

#### ETHICS COMMITTEE APPROVAL

The study was approved by the National Research Ethics Service: Semi-structured interviews: IRAS ID 183034, CPMS study ID 20368, adopted January 2016; Delphi and consensus meeting: IRAS ID 215791, CPMS Study ID: 33052; adopted February 2017.

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